REMARKS

The present application is directed to a method of detecting the presence of a target nucleic acid in a sample. Claims 1-42 were cancelled by a previous amendment. Claims 72-76 were withdrawn by a previous amendment as being drawn to a non-elected invention. As a result of this amendment, Claims 43-71 are amended, Claim 84 is cancelled, and Claims 85-86 are newly added. Upon entry of this amendment, Claims 43-71 and 85-86 will be pending in the application. No new matter is added.

Objection to the Specification

In the Office Action mailed September 28, 2007, the Examiner objected to the title of the invention. By this amendment, the title has been changed to "Methods for Detecting Target Nucleic Acid Molecules". In light of this amendment, applicants respectfully request withdrawal of the objection.

Rejection under 35 U.S.C. §112, second paragraph

In the Office Action mailed September 28, 2007, the Examiner rejected Claim 44 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which applicants regard as the invention. By this amendment, Claim 44 has been amended to remove the word "agents", which is replaced with the singular form, "agent", as in Claim 43. In light of this amendment, applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §102(b)

In the Office Action mailed September 28, 2007, the Examiner rejected Claim 84 under 35 U.S.C. §102(b) as anticipated by Fisher et al., (U.S. Pat. No. 5,491,063). By this amendment, Claim 84 has been cancelled. In light of this amendment, applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102(b).

Rejection under 35 U.S.C. §102(e)

In the Office Action mailed September 28, 2007, the Examiner rejected Claims 43-44, 48-55, and 57-69 under 35 U.S.C. §102(e) as anticipated by Lee (US 2004/0241679, hereinafter "Lee"). Applicants respectfully traverse this rejection.

Claim 43 is amended herein to specify that the DNA duplex binding agent can absorb fluorescent energy from the fluorescent label on the probe, but that the DNA duplex binding agent emissions **are not detectable in the context of the method**. Claim 66 is also amended herein to clarify that the DNA duplex binding agent **does not emit radiation in the visible range of the spectrum**. The assay described in Lee requires fluorescence energy transfer ("FET") or fluorescence resonance energy transfer ("FRET") to occur. Generally speaking, for both types of those reactions to occur, both the donor and acceptor label fluoresce to some extent during the course of the process. Therefore, the emissions would be detectable because there would be fluorescent emissions. In contrast, the method of the present application uses a DNA duplex binding agent whose emissions are not detectable in the context of the claimed method. Applicants respectfully submit that there is no suggestion in Lee that the DNA binding agent should be selected so that its emissions are not detectable in the context of the method. In fact, the converse is true. See, for example, paragraph [0036] of Lee, which suggests that in a preferred embodiment the DNA duplex binding agent should be the **donor** in the system. In that case, the DNA duplex binding agent would be required to emit light in a detectable manner, since it would be required to excite the acceptor label on the probe.

The Examiner refers to paragraph 43, page 4 of Lee, which lists some acceptor labels that may be used in the method of Lee, including some "dark" acceptors such as DABCYL, methyl red, QSY-7 diarylrhodamine dyes and 6-(methylamino)-2-[4-[4 (dimethylamino) phenyl]-1,3-butadienyl]-1-ethyl quinlinium perchlorate. However, one of ordinary skill in the art would appreciate that **none of these reagents are able to function as DNA duplex binding agents**, and therefore would not be of use in the method as claimed in

the present application. As noted on page 2, lines 29-33, of the specification of the present application, it is advantageous to use a DNA duplex binding agent such as an intercalating dye and a probe which is singly labeled because these components are much more economical than other assays in which double labeled probes are required. Furthermore, because only one probe is used, the length of known sequence necessary to form the basis of the probe can be relatively short so that the method of the present application can be used even in difficult diagnostic situations.

Furthermore, as noted on page 4, lines 6-15 of the instant application, the claimed method is also superior because by using a DNA duplex binding agent that is selected on the basis that its emissions are not detectable in the context of the method, the common problem with the DNA duplex binding agent supplying a signal that may overlap with that of the probe is avoided. Consequently, the need to resolve the signals from the probe from the signals from the DNA duplex binding agent is eliminated. As a result, a broader bandwidth over which a meaningful signal can be measured is available.

Consequently, applicants respectfully submit that Lee fails to disclose a method using a DNA duplex binding agent as the acceptor, where the DNA duplex binding agent is selected on the basis that its emissions are not detectable in the context of the method. Because Lee does not disclose each and every element of the claims of the present application, it fails to anticipate the claims. Claims 33, 48-55, and 57-65 depend directly or indirectly on Claim 43, and Claims 67-69 depend directly or indirectly on Claim 66. As a result of the amendments to Claim 43 and Claim 66, the dependent claims are also free of the prior art. In light of the amendments to the claims and the forgoing remarks, applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102(b) .

Rejection under 35 U.S.C. §103(a)

In the Office Action mailed September 28, 2007, the Examiner rejected Claims 43-44, 48-69, and 84 under 35 U.S.C. §103(a) as obvious over Lee et al. (WO 99/28500, hereinafter "Lee II") in view of Marrazza et al. ("Disposable DNA

electrochemical sensor for hybridization detection," Biosensors and Bioelectronics, 1999, Vol. 14, pp. 43-51, hereinafter "Marrazza"). Applicants respectfully traverse this rejection.

As discussed above, Claim 43 has been amended to specify that the DNA duplex binding agent used in the method can absorb fluorescent energy from the fluorescent label on the probe but the emissions of the DNA duplex binding agent **are not detectable in the context of the method**. Claim 66 has also been amended to clarify that the DNA duplex binding agent **does not emit radiation in the visible range of the spectrum**. Applicants agree with the Examiner that Lee II does not discuss a method wherein the DNA duplex binding agent does not emit visible light. Furthermore, applicants respectfully submit that Lee II also does not discuss a method wherein the DNA duplex binding agent can absorb energy from the fluorescent label on the probe but the emissions of the DNA duplex binding agent are not detectable in the context of the method. Marrazza does not satisfy this deficiency. In Marrazza, daunomycin hydrochloride is used as an electroactive indicator, which intercalates double-stranded DNA hybrids as they are formed (see page 43). The potential value of the daunomycin anodic peak is used to detect the presence and amount of the hybrid sequences formed (see page 44). Marrazza describes an "anodic peak potential shift of daunomycin toward more positive values" that is measured during the reaction; therefore, there is a difference in the potential value of the daunomycin depending whether a hybridized oligonucleotide or a single stranded oligonucleotide is present in the sample (see page 47). In other words, the daunomycin is being used as the **DNA duplex binding agent**, and its electrochemical emissions are being detected and measured in order to monitor the reaction. Applicants respectfully submit that this fails to satisfy the limitation of Claim 43, wherein the DNA duplex binding agent emissions are not detectable in the context of the method since the electrochemical emissions of the daunomycin are being detected in the context of the method used in Marrazza.

Marrazza also fails to describe any of the components used in its method as **fluorescence absorbers**, or to describe them as being able to take part in FET or FRET exchanges in any way. Therefore, applicants respectfully submit that it would not have been

obvious to apply the DNA intercalators described in Marrazza in the method of Lee II. Furthermore, Marrazza describes a highly complex assay which is carried out on a surface and requires the use of a complex series of steps. Consequently, one of ordinary skill in the art would not look to a reference like Marrazza for combination with Lee II.

Neither Lee II nor Marrazza, alone or in combination, satisfies all the limitations of the claims of the present application. Claims 44 and 48-65 depend directly or indirectly on Claim 43, and Claims 67-69 depend directly or indirectly from Claim 66. Claim 84 has been cancelled. As a result of the amendments to Claim 43 and Claim 66, the dependent claims are also free of the prior art. In light of the amendments to the claims and the above remarks, applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a).

In the Office Action mailed September 28, 2007, the Examiner rejected Claims 43-46 and 48-70 under 35 U.S.C. §103(a) as obvious over Lee II in view of Yun et al. (U.S. Pat. No. 7,090,977 B2, hereinafter "Yun"). Applicants respectfully traverse this rejection.

Lee II has been discussed above. Nothing in Yun satisfies the deficiencies of Lee II. Yun describes a method for detecting nucleic acid hybridization by using a series of compounds, including a nucleic acid intercalator, to induce an electrochemiluminesence reaction and detecting the quantity of light that is generated by this reaction. The reference is silent as to whether or not a visible fluorescent signal is emitted by the DNA duplex binding agent itself. Clearly, however, **a visible signal is generated by the reaction described in Yun** and is detected by an optical detector (see column 4, line 14). Yun does not, however, describe any of the components used in its method as **fluorescence absorbers**, or describe them as being able to take place in FET or FRET exchanges in any way. It would not have been obvious, consequently, to use the DNA intercalators described in Yun in the method of Lee II. Furthermore, Yun specifically states that its method can be used without a label (see abstract). This is directly opposed to the claims of the present application, which require the use of a **fluorescent label on a probe**.

Neither Lee II nor Yun, alone or in combination, satisfies all the limitations of the claims of the present application. Claims 44-46 and 48-65 depend directly or indirectly from Claim 43, and Claims 67-70 depend directly or indirectly from Claim 66. As a result of the amendments to Claim 43 and Claim 66, the dependent claims are also free of the prior art. In light of the amendments to the claims and the above remarks, applicants respectfully assert that this rejection has been overcome and request its withdrawal.

In the Office Action mailed September 28, 2007, the Examiner rejected Claims 45-47 and 70-71 under 35 U.S.C. §103(a) as obvious over Lee II in view of Marrazza as applied to Claims 43-44, 48-69 and 84 as described above, and further in view of Patterson (U.S. Pat. No. 5,132,327, hereinafter "Patterson"). Applicants respectfully traverse this rejection.

Applicants understand the Examiner to mean that because Marrazza describes certain compounds which are useful in detection of nucleic acids and which also happen to have anti-cancer activity, then it would be obvious that **any** other anti-cancer compound would also have a similar usefulness in detection of nucleic acids. Applicants respectfully disagree. The teaching of Marrazza is that the particular physical properties of certain compounds, in particular electrochemical properties, may be used in certain assays for detection. These properties are largely independent of any biological properties, such as anti-cancer properties, that these compounds may have. Patterson solely describes compounds that are useful for the treatment of cancer, and as such adds nothing regarding compounds useful in assays for detection of nucleic acids to the disclosure of Marrazza. Therefore, it would not have been obvious to one of ordinary skill in the art to suggest that other anti-cancer compounds would have similar detection properties in terms of factors such as electrochemical effect on the basis of Patterson. One of ordinary skill in the art would not have selected a compound for use in a detection method simply because of the compound's anti-cancer properties. In light of the above remarks, applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a).

In the Office Action mailed September 28, 2007, the Examiner rejected Claims 47 and 71 under 35 U.S.C. §103(a) as obvious over Lee II in view of Yun as applied to claims 43-46 and 48-70 as described above, and further in view of Patterson.

Applicants understand the Examiner to mean that because Yun describes certain compounds which are useful in detection of nucleic acids and which also happen to have anti-cancer activity, then it would be obvious that **any** other anti-cancer compound would also have a similar usefulness in detection of nucleic acids. Applicants respectfully disagree. The teaching of Yun is that the particular physical properties of certain compounds, in particular electrochemiluminescent properties, may be used in particular assays for detection. These properties are largely independent of any biological properties, such as anti-cancer properties, that these compounds may have. Patterson solely describes compounds that are useful for the treatment of cancer, and as such adds nothing regarding compounds useful in assays for detection of nucleic acids to the disclosure of Yun. Therefore, it would not have been obvious to one of ordinary skill in the art to suggest that other anti-cancer compounds would have similar detection properties in terms of factors such as electrochemiluminescent effect on the basis of Patterson. One of ordinary skill in the art would not have selected a compound for use in a detection method simply because of the compound's anti-cancer properties. In light of the above remarks, applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a).

Neither Lee II, Marrazza, Yun, nor Patterson, alone or in combination, satisfies all the limitations of the claims of the present application. In light of the amendments to the claims and the above remarks, applicants respectfully assert that this rejection has been overcome and request its withdrawal.

Double Patenting

In the Office Action mailed September 28, 2007, the Examiner provisionally rejected Claims 43-44 and 48-69 on the grounds of nonstatutory obviousness-type double patenting over Claims 1-4, 6-7, 9, and 10-14 of copending Application No. 10/478,788.

Applicants respectfully submit that the claims as amended herein are patentably distinct from copending Application 10/478,788 because the emissions of the DNA duplex binding agent are not detectable in the context of the method of the present application. Accordingly, applicants respectfully request withdrawal of the provisional rejection.

In the Office Action mailed September 28, 2007, the Examiner rejected Claims 43-46 and 48-70 on the grounds of nonstatutory obviousness-type double patenting over Claims 1-2, 4-9, and 11-13 of U.S. Pat. No. 6,833,257 (described above as "Lee II") in view of Yun. Applicants respectfully traverse this rejection. Applicants respectfully submit that the claims as amended herein are patentably distinct from Claims 1-2, 4-9, and 11-13 of Lee II in view of Yun because the emissions of the DNA duplex binding agent are not detectable in the context of the method of the present application. The basis of the method described in the present application is that the DNA duplex binding agent is an acceptor specifically selected so that during the course of the method it does not emit a signal which interferes with that of the label. The existence of such compounds and a description of how to use them in this matter is not taught in any of the cited references. Yun suggests compounds that may be used in the context of an electrochemiluminiescent assay, but this is different from a fluorescence assay. See, in particular, column 1, lines 30-45, of Yun which specifically discusses disadvantages of fluorescent techniques. Consequently, the present claims are patentably distinct from Lee II and Yun. Accordingly, applicants respectfully request withdrawal of the rejection.

CONCLUSION

This response fully addresses the rejections in the Office Action of September 28, 2007. In light of the above remarks, applicants respectfully assert that the application is now in condition for allowance. Such action is respectfully requested.

If the Examiner believes any informalities remain in the application that may be corrected by Examiner's Amendment, or if there are any other issues that can be resolved by telephone interview, a telephone call to the undersigned agent at (404) 815-6473 is respectfully solicited.

No additional fees are believed due; however the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account number 11-0855.

Respectfully submitted,

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